WASHINGTON STATE DEPT. OF LABOR AND INDUSTRIES
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CLINICAL GUIDANCE FOR EVALUATING BERYLLIUM SENSITIZATION AND CHRONIC BERYLLIUM DISEASE

PURPOSE

This guidance provides the clinical criteria and case definitions for beryllium sensitization (BeS) and chronic beryllium disease (CBD; old term = berylliosis), based on the latest available medical literature and consultation with leading experts in the field. It describes how the department and self-insurer evaluate claims for beryllium sensitization and CBD. This guidance does not address exposure prevention and workplace safety.

BACKGROUND

Beryllium is a lightweight alkaline metal occurring naturally in soils and in coal; [1] it is processed into metals oxides, alloys, and composite materials. [2] Exposure to beryllium usually occurs through the inhalation of beryllium-containing dust, particles, vapor, liquids or fumes, though skin contact can also manifest as dermatitis and ulcerations with poor wound healing. [1] Chronic disease is due to a cell-mediated sensitization response. [2-4] There is currently no vaccine or post-exposure prophylaxis for beryllium exposure.

Certain occupations or work environments place workers at increased risk for exposure to beryllium and beryllium-containing substances. There is evidence that even minimal exposures can lead to BeS and CBD. [2]

Table 1. Industries and Occupations with Potential Beryllium Exposure [2, 5-9]

Industries	**Occupations**
Atomic energy/nuclear industries including power, weapons & defense	Grinders
Metal working (with Be-containing metals)	Machinists
Rod and wire and copper tubing production	Hot press operators
Aeronautics/aerospace	Welders
Electronics & computers manufacturing	Security Guards where there is known risk of exposure
Construction/demolition	Janitorial workers where there is known risk of exposure
Ceramic manufacturing	Dental hygienists, prosthetists, technicians
Laboratory work	Laser cutters of beryllium metals and alloys
Recycling/ Hazardous waste cleanup	Those who worked with fluorescent lamps prior to 1951
Fiber optics	Those who decontaminate or decommission structures where beryllium was present/used.
Dental materials manufacturing and laboratories (alloys in bridges, crowns etc.)	Cleaners or rebuilders of furnaces where beryllium was present/used
Bicycle and golf club manufacturing	
Plastics injection molding	

BERYLLIUM SENSITIZATION

Sensitization to beryllium is an immunologic response at a cellular level and is dependent on host factors and exposure factors. Host factors refer to a genetic susceptibility for having immune-mediated response to beryllium. Genetic testing is not a suitable screening test because the prevalence of the genetic susceptibility is high in the general population. [9] The amount or duration of exposure needed to develop sensitization is not known. "CBD can occur among those judged to have had trivial, unrecognized, or brief exposure to beryllium". [3] Medical literature states "it is not possible to identify an occupational exposure limit that will prevent all cases of CBD". [10] The prevalence of sensitization to beryllium has been observed to vary by industry and job or process type. [3]

The standard test for beryllium sensitization is the beryllium lymphocyte proliferation test (BeLPT), which can be performed on either a blood sample or fluid obtained via bronchoalveolar lavage (BAL). Before the BeLPT test was available, a skin patch test was used, but this test is not required by Labor and Industries (L&I) because the test itself can induce beryllium sensitization in previously un-sensitized individuals. [2, 4] The bronchoalveolar lavage LPT is considered especially useful diagnostically when evaluating for CBD in the setting of negative blood LPTs, though cigarette smoking and immunosuppressants can cause false negative results in BeLPT tests obtained from BAL. [2, 9]

The case definition L&I uses to define work-related beryllium sensitization requires that all of the following criteria be met:

1. There is a work-related history of beryllium exposure — regardless of duration or amount — on a more-probable-than-not basis. Work-relatedness of exposure is established by either a, b, or c:
   a. If the exposure resulted from a direct occupational injury such as a puncture wound from beryllium metal, OR
   b. If the exposure is <u>not</u> due to an occupational injury, but arises from conditions that are distinctive to the job (e.g. working in an environment where known beryllium-containing alloys, dust, vapors, or liquids are present), OR
   c. The worker does not have a documented exposure to beryllium, but is found to be sensitized per the criteria in section two (below). These workers are presumed to have sustained exposure to beryllium because evidence shows beryllium exposure may be unrecognized, and minimal exposures can lead to BeS and CBD. [2] Evaluating work-relatedness of undocumented exposure should be based on careful analysis and exposure assessment, such as that available at a center for chemically-related illness. Contact L&I Office of the Medical Director for referral assistance.
2. Beryllium sensitization is confirmed by:
   a. At least two abnormal blood BeLPT tests* [2] OR
   b. At least one abnormal and one borderline blood BeLPT tests* [2] OR
   c. At least three borderline blood BeLPT tests*† [2, 11] OR
   d. An abnormal bronchoalveolar lavage LPT if performed [2] OR

e. Positive skin patch test to beryllium if performed [2]. Labor and Industries does not require skin patch testing to diagnose chronic beryllium disease due to the risk of inducing sensitization. [2, 4]

* Obtaining at least two tests improves the accuracy of test results. [11-13] Blood BeLPT testing algorithms obtain higher sensitivity by splitting the initial blood sample between two laboratories, while keeping the risk of a false positive low. [12] Labor and Industries therefore recommends splitting the initial peripheral blood sample when performing BeLPT testing in circumstances where ongoing serial testing is not assured. [12]

† Middleton et al determined that the predictive value of three borderline results was higher than the minimum three result combination that meets criterion 2 b (1 abnormal + 1 borderline + 1 normal LPT). [11]

CHRONIC BERYLLIUM DISEASE

Chronic beryllium disease (CBD) is a granulomatous disease that most often manifests in the lungs, although rarely it affects other organs such as the liver, spleen, lymph nodes, heart, kidneys, and salivary glands. [1, 4] Although studies of exposure-response are inconsistent, there is evidence of association between increased exposure to beryllium and developing CBD. [2] There is also evidence that the OSHA 2.0 $\mu g/m^3$ standard does not protect against developing CBD. [2, 10] The period between the first beryllium exposure and the onset of CBD ranges from months to decades. [7, 14, 15]

Because the symptoms of CBD are mostly respiratory in nature, it can be confused with other possible diagnoses such as sarcoidosis, idiopathic pulmonary fibrosis, hypersensitivity pneumonia, asthma, and other granulomatous lung diseases. [9, 16]

The case definition L&I uses to define work-related CBD follows that of the 2014 Official American Thoracic Society (ATS) Statement: Diagnosis and Management of Beryllium Sensitivity and Chronic Beryllium Disease. [2]

<u>Definitive work-related CBD requires</u>:

1. Evidence of work-related beryllium sensitization as defined above, AND
2. EITHER:
   a. Lung biopsy showing granulomatous inflammation (typically noncaseating granulomas), OR
   b. Clinical presentation and diagnostic findings consistent with CBD, such as from imaging studies, bronchoalveolar lavage, and pulmonary function tests.

In rare circumstances, following comprehensive evaluation as described above (including bronchoalveolar lavage BeLPT unless medically contraindicated), CBD may be present without a positive BeLPT test. For example, the BAL BeLPT can be falsely negative in cigarette smokers.[16] In these rare circumstances, a diagnosis of work-related CBD may be made if <u>all four</u> of the following criteria are met:

1. There is a known scientific or medical basis for the false negative BeLPT result, AND
2. The patient has a clinical presentation and objective findings consistent with CBD, e.g. a lung biopsy confirming the presence of granulomas that are consistent with CBD, AND
3. Other causes of granulomatous lung disease have been excluded, such as mycobacterial and fungal infection; hypersensitivity pneumonitis; and sarcoidosis with systemic disease and extra-pulmonary organ involvement (e.g. neurologic, ophthalmologic, cardiac, etc.), AND
4. There is strong evidence of work-related exposure to beryllium, e.g. through a documented occupational injury, exposure monitoring demonstrating exposure distinctive to employment, or confirmed cases of work-related beryllium sensitization in similarly exposed co-workers of the individual.

CLINICAL SYMPTOMS OF CBD

Signs, symptoms and test results of CBD can include [5, 9, 17]:

Per History and Physical

- Non-productive cough
- Abnormal lung sounds (crackles)
- Chest discomfort
- Dyspnea on exertion
- Fever
- Weight loss
- Night sweats
- Fatigue
- Loss of appetite

Per Tests and Procedures

- Chest x-ray or CT scans show small lung scars, hilar adenopathy (enlargement of lymph nodes in the central part of the chest), and/or most commonly reticular-nodular infiltrates
- Abnormal results from pulmonary function tests, such as restrictive, obstructive, or mixed patterns, or showing restrictive patterns or reduced carbon monoxide diffusing capacity
- Hypoxemia by arterial blood gases or oximetry, and oxygen desaturation with exercise
- Granulomas found in lung or skin tissue per biopsy
- Lymphocytosis on bronchoalveolar lavage

TREATMENT FOR CHRONIC BERYLLIUM DISEASE

In addition to removal from beryllium exposure, treatment for CBD is largely supportive care based on the degree of symptom severity, functional lung impairment, and the degree of tissue involvement as determined by imaging or biopsy. Typical treatment includes glucocorticoids or other immunosuppressive agents. Though their efficacy has not been tested in controlled clinical trials, it is believed that the chance of improvement is best if these therapies are started before fibrotic changes occur in the lungs. Other immunosuppressive medications may also be tried e.g. methotrexate and azathioprine, but adverse side effects of long term use of any agents will have to be weighed against the benefits and the clinical progression of the disease. It is also recommended to provide influenza and pneumonia vaccinations, and smoking cessation counseling to help minimize respiratory symptoms and reduce the chance of complications.[9]

FOLLOW-UP FOR BERYLLIUM SENSITIZED WORKERS

Chronic beryllium disease can be present without obvious symptoms, and the latency between exposure and manifestation of disease ranges from months to decades. [7, 14, 15] Because of this long latency, workers might file an initial claim several years after a work-related exposure, or might need to re-open a claim filed years before, to receive care for their beryllium-related condition.

Workers with beryllium sensitization require periodic medical evaluation to monitor for progression to chronic beryllium disease, at least every 2-3 years, and more frequently if clinical concern requires. [2,18] Patients with known chronic beryllium disease are usually evaluated more frequently, e.g. at least annually or more often according to clinical need. [2,19]

REFERENCES

1. Newman, L.S., *Hazardous Materials Toxicology, Clinical Principles of Environmental Health* ed. J.B. Sullivan1992: Willams & Wilkins.
2. Balmes, J.R., Abraham, J.L., Dweik, R.A., Fireman, E., Fontenot, A.P., Maier, L.A., Muller-Quernheim, J., Ostiguy, G., Pepper, L.D., Saltini, C., Schuler, C.R., Takaro, T.K., and Wambach, P.F., *An official American Thoracic Society statement: diagnosis and management of beryllium sensitivity and chronic beryllium disease.* Am J Respir Crit Care Med, 2014. **190**(10): p. e34-59.
3. Kreiss, K., Day, G.A., and Schuler, C.R., *Beryllium: a modern industrial hazard.* Annu Rev Public Health, 2007. **28**: p. 259-77.
4. Balmes, J.R., *Textbook of Clinical Occupational and Environmental Medicine*. Second ed. Chronic Beryllium Disease and Cobalt-Related Interstitial Lung Disease (Hard-Metal Disease and Diamond Polisher's Lung Disease)2005: Philadelphia, PA, USA: Elsevier Saunders.
5. Seidler, A., Euler, U., Muller-Quernheim, J., Gaede, K.I., Latza, U., Groneberg, D., and Letzel, S., *Systematic review: Progression of beryllium sensitization to chronic beryllium disease.* Occup Med (Lond), 2012. **62**(7): p. 506-13.
6. Rossman, M.D., *Differential Diagnosis of Chronic Beryllium Disease*. Beryllium: Biomedical and environmental aspects ed. G.T. Minton1991: Williams and Wilkins.
7. Mayer, A.S., Hamzeh, N., and Maier, L.A., *Sarcoidosis and chronic beryllium disease: similarities and differences.* Semin Respir Crit Care Med, 2014. **35**(3): p. 316-29.
8. Hospital., T.M.S. *Berylliosis Information* July 11th 2014]; Available from: http://www.mountsinai.org/patient-care/health-library/diseases-and-conditions/berylliosis.
9. Newman, L.S., Maier L, in *Chronic beryllium disease (berylliosis)*, P. TW., Editor 2014, UpToDate: Waltham MA.
10. Michaels, D. and Monforton, C., *Beryllium's public relations problem: protecting workers when there is no safe exposure level.* Public Health Rep, 2008. **123**(1): p. 79-88.
11. Middleton, D.C., Mayer, A.S., Lewin, M.D., Mroz, M.M., and Maier, L.A., *Interpreting borderline BeLPT results.* Am J Ind Med, 2011. **54**(3): p. 205-9.
12. Middleton, D.C., Lewin, M.D., Kowalski, P.J., Cox, S.S., and Kleinbaum, D., *The BeLPT: algorithms and implications.* Am J Ind Med, 2006. **49**(1): p. 36-44.
13. Middleton, D.C., Fink, J., Kowalski, P.J., Lewin, M.D., and Sinks, T., *Optimizing BeLPT criteria for beryllium sensitization.* Am J Ind Med, 2008. **51**(3): p. 166-72.
14. Kelleher, P.C., Martyny, J.W., Mroz, M.M., Maier, L.A., Ruttenber, A.J., Young, D.A., and Newman, L.S., *Beryllium particulate exposure and disease relations in a beryllium machining plant.* J Occup Environ Med, 2001. **43**(3): p. 238-49.
15. Eisenbud, M. and Lisson, J., *Epidemiological aspects of beryllium-induced nonmalignant lung disease: a 30-year update.* J Occup Med, 1983. **25**(3): p. 196-202.

16. Kreiss, K., Miller, F., Newman, L.S., Ojo-Amaize, E.A., Rossman, M.D., and Saltini, C., *Chronic beryllium disease--from the workplace to cellular immunology, molecular immunogenetics, and back.* Clin Immunol Immunopathol, 1994. **71**(2): p. 123-9.
17. National Jewish Health MEDfacts 2004 October 2014]; Available from: http://www.nationaljewish.org/getattachment/47c56a62-34f5-47f5-9cb3-d79d0e45309c/pdf-MF-Beryllium-Disease.pdf.aspx?ext=.pdf.
18. Wang, M.L., Avashia, B.H., and Petsonk, E.L., *Interpreting periodic lung function tests in individuals: the relationship between 1- to 5-year and long-term FEV_1 changes.* Chest, 2006. **130**(2): p. 493-9.
19. Sood, A., *Current Treatment of Chronic Beryllium Disease.* Journal of Occupational and Environmental Hygiene, 2009. **6**: p. 762-5.